DIPHENHYDRAMINE TANNATE LIQUID AND SEMI-SOLID COMPOSITIONS AND METHODS OF USE

This is a continuation-in-part of U.S. Patent Application Serial No. 10/119,285 filed April 9, 2002 which claims the benefit of Provisional Patent Application Serial No. 60/282,969 filed April 10, 2001.

Field of Invention

The invention relates to novel antihistaminic tannate compositions. The compositions contain as an essential ingredient diphenhydramine tannate.

Background of the Invention

Tannins are water-soluble phenolic metabolites of plants with a molecular weight of 5 - 5000 Da. Physicochemically, tannins are complex polymers, which can be classified as two major types: the condensed tannins and hydrolyzable tannins. Hydrolyzable tannins or tannic acids are referenced in the various pharmacopeias and are composed of gallic acid or its condensation product ellagic acid esterified to the hydroxyl groups of

glucose. Each hydrolyzable tannin molecule is usually composed of a core D-glucose and 6 to 9 galloyl groups.

In nature, there is an abundance of mono and di-galloyl esters of glucose with a molecular weight of about 900. These are not considered to be tannins. At least 3 hydroxyl groups of the glucose must be esterified to exhibit a sufficiently strong binding capacity to be classified as tannin.

Tannic acid, also known as tannin, is commercially available with a water content of about 5% to about 10% by weight and a molecular weight of about 1700. It is typically produced from Turkish or Chinese nutgall and has a complex, non-uniform chemistry.

Diphenhydramine is known chemically as 2-(benzhydroxyl)-N,N-dimethylethylamine. The methods of preparation of the drug are described in U.S. Patent Nos. 2,421,714 and 2,397,799. Diphenhydramine Hydrochloride salt has a melting point of 166-170 degrees C and is soluble in water and sparingly soluble in alcohol. The pH of a 1% aqueous solution is about 5.5. Diphenhydramine belongs to the class of ethanolamine H1 receptor blockers, and possesses in addition to antihistaminic activity, a significant anticholinergic effect, which makes it highly effective for the symptomatic relief of sneezing, itchy, watery eyes, itchy nose or throat and runny nose due to hay fever (allergic rhinitis) and other respiratory allergies. It has lower incidences of gastrointestinal side effects than compositions containing other antihistamine compounds by themselves or in combination with diphenhydramine. Diphenhydramine also possesses a pronounced tendency to induce sedation.

Antihistamine compounds in the form of their free bases as well as their salts, e.g. hydrochloride, maleate, tannate, etc. are well known. Frequently it is desirable to utilize the antihistamine in the form of its

tannate salt, because such salt is generally quite stable and may be administered in such form without any side effects. In addition, the tannate salt of the active is a significantly larger molecule, which affords absorption of the active over prolonged intervals of time, reducing the sedative action, frequency of administration and thereby improves patient compliance in comparison to other salt forms of antihistamines.

Antihistamines in the form of their tannate salts can be prepared by following a number of different procedures. In a first approach, the free base, e.g. diphenhydramine, etc. is reacted with tannic acid in the presence of a volatile solvent, isopropanol. Typically, in the conventional isopropanol route, the antihistaminic free base and the tannic acid will be present in the isopropanol at a concentration based on the weight of the reaction mixture. The reaction mixture is stirred for about one hour while maintaining the mixture at 60-70 degrees C. The reaction mixture is cooled to room temperature and then filtered, washed with isopropanol and then vacuum dried. However, antihistamine tannate salts are heat sensitive and therefore undergo decomposition quite readily upon prolonged exposure to temperatures as low as 50 degrees C. In addition, the yield obtained is usually only about 70% and impurities including decomposition products and a significant amount of the volatile solvent used during preparation (up to about 5-10%) cannot be effectively removed.

Further, due to the large size of the tannate molecule, the percentage of active free-base within the tannate salt is significantly lower than that in other salt forms such as the hydrochloride or maleate. The presence of low active percentages and the variable purity of the tannate compounds prepared by these synthetic methods leads to the stoichiometry of the active free base to tannic acid in the tannate salts to be different from batch to

batch. This causes significant processing problems during manufacture of products containing tannate salts as active ingredients, and increases the likelihood that commercially available pharmaceutical products contain variable and in some instances, sub-therapeutic levels of said active drug substances creating dosing problems. Decomposition products of diphenhydramine resulting from exposure to higher temperatures associated with this first production approach include benzhydrol, benzophenone, diphenylchloromethane, dimethylaminoethanol, diphenylmethane, and diphenyl alkyl ether.

A second approach to prepare the antihistamine tannates, is to contact the free base form of the drug with tannic acid in the presence of water for a suitable period of time and at a maximum temperature. The antihistamine tannate salt is usually isolated and purified by freeze-drying and then subsequently introduced into pharmaceutically effective dosage forms. This approach results in a dosage form suffering from a number of shortcomings. These include the use of expensive equipment and the time involved in freeze-drying. This approach also suffers from batch to batch variability and all of the attendant disadvantages outlined above. Further, the development of a suitable and effective freeze-drying process can be complicated.

A third and better approach to prepare the antihistamines in the form of their tannate salts is disclosed in our copending U.S. Patent Application serial no. 10/119,285 filed April 9, 2002, entitled "Process For Preparing Tannate Liquid And Semi-Solid Dosage Forms", the full disclosure of which is incorporated herein by reference. In this approach, an aqueous solution or the powder form of the drug is reacted with a tannic acid mixture in liquid or powder form. The tannate salt prepared by this method

can be isolated and purified by filtration, drying or centrifugation or can be directly incorporated into suitable pharmaceutically effective dosage forms without the need for further isolation or purification. In addition, the exposure of the tannate salts to high temperatures that can produce undesirable decomposition products, is also avoided.

The tannate salt of the antihistamine can also be prepared without the use of organic solvents, which would be desirable from an environmental standpoint. This also allows one to eliminate organic solvents as a possible contaminant in the final dosage product. In addition, a commercially available USP/NF grade salt or the free base of the antihistamine can be used with USP/NF grade tannic acid to prepare the tannate salt. This insures that the stoichiometry of the active ingredient may be properly matched to the tannic acid. As a result, the potency of the finished product is less variable and, therefore, more precise dosing is possible. Patient benefits include more effective treatment with minimal unwanted or adverse side effects.

Summary of the Invention

The present invention relates to a therapeutic composition for symptomatic treatment of respiratory allergies in a warm-blooded animal where that composition comprises a pharmaceutically effective amount of diphenhydramine tannate of consistent purity in the substantial absence of an organic solvent. That organic solvent may, for example, be a mineral oil or an alcohol including but not limited to such solvents as isopropyl alcohol, glycerine, propylene glycol and ethanol.

Alternatively, the invention may be described as a therapeutic composition for symptomatic treatment of respiratory allergies in a warm-

blooded animal where the composition comprises a pharmaceutically effective amount of diphenhydramine tannate of consistent purity in substantial absence of decomposition products of diphenhydramine tannate produced at temperatures above about 50 degrees C. Such decomposition products include but are not necessarily limited to benzhydrol, benzophenone, diphenylchloromethane, dimethylaminoethanol, diphenylmethane and diphenyl alkyl ether.

Still further the therapeutic composition may be defined as comprising a pharmaceutically effective amount of diphenhydramine tannate of consistent purity prepared in a preferred way by:

(a) dissolving the salt or free base of the diphenhydramine in a pharmaceutically acceptable liquid to form a solution at a maximum temperature and pH value, that does not cause decomposition of the active pharmaceutical ingredient;

(b) separately adding a dispersing agent and tannic acid to a pharmaceutically acceptable liquid, under stirring, to form a dispersion;

(c) transferring the solution from step (a), in portions to the dispersion in step (b) under stirring, to form a precipitate of a tannate salt of diphenhydramine; and

(d) combining the tannate salt of the diphenhydramine without isolation or purification with pharmaceutically acceptable excipients to generate a therapeutic dosage form.

In accordance with yet another aspect of the present invention, a method is provided for symptomatically treating respiratory allergies in a warm-blooded animal. That method comprises administering to the warm-blooded animal a pharmaceutically effective amount of diphenhydramine tannate of consistent purity in substantial absence of an organic solvent.

Alternatively, the method may be described as comprising administering to the warm-blooded animal a pharmaceutically effective amount of diphenhydramine tannate of consistent purity in substantial absence of decomposition products of diphenhydramine tannate produced at temperatures above about 50 degrees C.

Still further the method may be described as comprising administering to the warm-blooded animal a pharmaceutically effective amount of diphenhydramine tannate of consistent purity prepared by:

(a) dissolving the salt or free base of the diphenhydramine in a pharmaceutically acceptable liquid to form a solution at a maximum temperature and pH value, that does not cause decomposition of the active pharmaceutical ingredient;

(b) separately adding a dispersing agent and tannic acid to a pharmaceutically acceptable liquid, under stirring, to form a dispersion;

(c) transferring the solution from step (a), in portions to the dispersion in step (b) under stirring, to form a precipitate of a tannate salt of diphenhydramine; and

(d) combining the tannate salt of the diphenhydramine without isolation or purification with pharmaceutically acceptable excipients to generate a therapeutic dosage form.

Detailed Description of the Invention

The present invention relates to a novel therapeutic composition in liquid or semi-solid dosage form containing a tannate salt of the active ingredient diphenhydramine at a consistent purity. The composition is prepared by a conversion process which includes the steps of mixing a dispersing agent and tannic acid in a suitable solvent to generate a mixture

in liquid form. The diphenhydramine as a salt or in the free base form is combined with the dispersing agent/tannic acid mixture to generate the tannate salt. The presence of the dispersing agent prevents the clumping and aggregation of the tannate salt formed and promotes uniformity in the solution. The formation of the tannate salt is by reaction of amine groups (in the 1°, 2°, 3°, 4°, or amphoteric functional states) or of the other basic functional groups with tannic acid. The amount and ratio of dispersing agent and tannic acid, required for the completion of the reaction, is determined by the molecular configuration and concentration of the diphenhydramine.

The tannate salt of diphenhydramine has been found to have better organoleptic properties such as taste, in comparison to other salts or free base forms. In addition, the tannate salt of diphenhydramine is a significantly larger molecule, which affords absorption of the diphenhydramine over prolonged intervals of time, reducing the frequency of administration and thereby reduces the sedative effect of diphenhydramine and improves patient compliance.

By starting with a known amount of commonly available salt or the free base form of the diphenhydramine, which is subsequently converted and incorporated in-situ as a tannate salt, the invention provides an efficient and reproducible method to manufacture products containing tannate salts as active ingredients. Since the tannate salt of the diphenhydramine is generated and incorporated in-situ into the dosage form during the manufacturing process, the purification and drying steps required for the isolation of the tannate salt are eliminated and the stoichiometry of the tannate salt is uniform from batch to batch. This is particularly true when using USP/NF grade starting materials. Thus, diphenhydramine tannate is

provided for the first time at a consistent purity.

The diphenhydramine ingredient used is the free base or salt having anionic functional groups such as bitartrate, maleate, citrate, chloride, bromide, acetate and sulfate. The source of the tannic acid is natural or synthetic.

The preferred dispersing agent is chosen from the group such as magnesium aluminum silicate, xanthan gum and cellulose compounds. The thickening agents employed include kaolin, pectin, xanthan gum and cellulose compounds.

The excipients commonly used in the formulations are as follows: sucrose, saccharin sodium and artificial flavor as flavoring agents; kaolin, pectin, xanthan gum, magnesium aluminum silicate (referred to as MAS), as thickening and anti-caking agents; glycerine as a co-solvent; sodium citrate, sodium phosphate monobasic and dibasic, citric acid, sodium benzoate and benzoic acid as pH adjusting and buffering agents; methylparaben as a preservative; FD&C Red No. 40 and FD&C Blue No. 1 as coloring agents, and purified water.

The salts of the diphenhydramine are preferably dissolved in purified water thereby avoiding any possibility of contaminating the final product with organic solvents. This leads to the dissociation of the salt into its free base and conjugate acid forms. Another solution containing excess tannic acid in purified water is prepared. While stirring at low speeds, the solution of the salt is added in small portion to the tannic acid solution. Because of the presence of excess tannic acid, the free base form reacts with the tannic acid to form the tannate salt .. Since the tannate salt formed is larger in size and has low solubility in purified water, it is usually precipitated from solution.

The salt or free base of the diphenhydramine is dissolved in purified water or other pharmaceutically acceptable liquid. Purified water is taken in a vessel and stirred. While stirring, MAS is added in small portions to obtain a dispersion. Once the MAS is dispersed, tannic acid is added to the mixture and stirred to form a uniform dispersion. The active ingredient solution is then added in small portions, under light stirring, to the MAS/tannic acid dispersion. After all of the solution is added, the volume may be made up to a desired volume with purified water and stirring is continued for a period of ten minutes. The MAS is used in this step to serve as an adherent or a solid support for the tannic acid molecules to facilitate the conversion process. In addition, it also prevents the clumping of the tannate salt formed, which aids in the isolation of the precipitate of the tannate salt formed from the solution. The dispersion containing the tannate salt is transferred to the suspending medium.

The transfer of the diphenhydramine tannate salt preparation to the suspension vehicle(s) is completed without isolation or purification. Typical suspension vehicles are prepared comprising excipients such as kaolin/pectin or xanthan gum as thickening agents. In addition, the suspending vehicles also consist of sweetening, flavoring, coloring, pH-adjusting and buffering agents, preservatives and co-solvents. The conversion of the diphenhydramine is viscous (3000-5000 cps). It is transferred to the suspending medium by pouring. The precipitate formed during the conversion is found to adhere slightly to the walls of the container and may be scraped into the suspending medium using a spatula. Purified water is used to wash the remainder of the material into the suspending medium. The conversions show significantly less adhesion to stainless steel containers than glass containers. Preferably the entire

process is completed while maintaining a pH range between about 2 to about 11 and while not exceeding a temperature of about 15 to about 40 degrees C so as to minimize or substantially avoid the production of decomposition products.

The present invention provides a composition comprising diphenhydramine tannate at a consistent purity for the treatment of the symptoms of sneezing, itchy, watery eyes, itchy nose or throat and runny nose due to hay fever (allergic rhinitis) or other respiratory allergies which is superior to compositions containing antihistamine compounds by themselves or in combination.

The compositions of the present invention may contain diphenhydramine tannate in the substantial absence of other active ingredients such as other tannate salts. Such compositions are particularly effective for treating symptoms commonly associated with respiratory allergies while avoiding adverse side effects including but not limited to gastrointestinal upsets. Such compositions are particularly useful in treating children as they avoid exposure of the patient to other drugs that are unnecessary to provide effective treatment.

For other applications, the compositions of the present invention may include diphenhydramine tannate in combination with therapeutic agents from pharmacological classes such as antihistamines, anticholinergics, sympathomimetics, decongestants, cough suppressants, antitussives and expectorants for the treatment of allergic and upper respiratory disorders and symptoms.

Examples of antihistamines that could be used in the combinations include but are not limited to carbinoxamine, chlorpheniramine, pyrilamine, pheniramine, phenindamine, bromodiphenhydramine, triplennamine,

cimetidine, ranitidine, and famotidine.

Examples of anticholinergics that could be used in the combinations include but are not limited to methscopolamine, neostigmine and physostigmine.

Examples of antitussives, cough suppressants and expectorants that could be used in the combinations include but are not limited to carbetapentane, dextropmethorphan and guaifenesin.

Examples of decongestants that could be used in the combinations include but are not limited to phenylephrine, pseudoephedrine, ephedrine, cyproheptadine, phenyltoloxamine and clemastine.

Examples of sympathomimetics that could be used in the combinations include but are not limited to phenylethylamine, phenylephrine, methoxyphenamine and methoxamine.

The compositions of the present invention may be prepared for oral administration in the form of elixirs, syrups and the preferred forms of suspensions formulated so that ideally each 5 mL (approximately 1 teaspoon) of suspension would contain approximately 0.1 to 300 mg, preferably 25 mg of diphenhydramine tannate, at a pH range of 2.0 - 9.0, preferably from 6.0 - 7.5.

Suspensions of the compositions of the present invention may be prepared, such that each 5 mL (one teaspoon) contains 25 mg of diphenhydramine tannate, preferably by reacting the aqueous solution or the powder form of the drug with a tannic acid mixture in liquid or powder form, without the use of volatile solvents. The tannate salt prepared can then be directly incorporated into suitable pharmaceutically effective dosage forms without further purification and isolation. The suspension formulations additionally contain sodium benzoate, coloring, natural and

artificial flavors, xanthan gum, magnesium aluminum silicate, methyl paraben, purified water, saccharin, sodium hydroxide, tannic acid and sucrose or sorbitol. Example 1, which is illustrative of a typical suspension formulation of the present invention, is prepared as follows:

EXAMPLE

Ingredient	Milligrams per 5 mL
Diphenhydramine Tannate	25.0
Xanthan gum	27.5
Magnesium Aluminum Silicate	40.0
Sodium Benzoate	5.0
Methylparaben	10.0
Sucrose	50.0
Saccharin Sodium	5.0
Glycerin	375.0
Artificial Strawberry Flavor	15.0
FD&C Red #40	3.0
Purified Water, USP (Deionized) adjust to 5 mL.	

Tannic acid may also be used for pH adjustment. Monobasic sodium phosphate, USP, and Dibasic sodium phosphate, USP, Anhydrous may also be included in the formula for pH adjustment.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The dosage administered will be dependent on the age, health and weight of the recipient, kinds of concurrent treatment, if any, frequency of treatment and effect desired. Typically, from about 25 to about 50 mg of the diphenhydramine are administered to adults and children over twelve years of age every four to six hours up to a maximum of about 300 mg in any twenty-four hour period. From about 12.5 to about 25 mg of the diphenhydramine are administered to children from about six to about twelve years of age every four to six hours up to a maximum of about 150 mg in any twenty-four hour period.

In summary, numerous benefits result from the compositions of the present invention. As produced, those compositions are essentially free of contaminates including organic solvents and heat decomposition products including but not limited to benzhydrol, benzophenone, diphenylchloromethane, dimethylaminoethanol, diphenylmethane and diphenyl alkyl ether. The compositions are also characterized by a relatively consistent stoichiometry and potency of active ingredient: that is consistent purity. Accordingly, they allow for more precise dosing, a particularly important benefit when used in treating young children.

It should be understood that the above examples are illustrative of the best mode only of the invention herein disclosed. Given the present disclosure, it is anticipated that numerous variations will occur to those skilled in the art. For example, the composition could be prepared for administration in a nasal spray form if desired. A latitude of modification, substitution and change is intended and in some instances, some features of

the invention will be employed without a corresponding use of other features. Accordingly, it is intended that the spirit and scope of the invention disclosed herein should be limited only by the following claims.